

**A PROCESS FOR THE PREPARATION OF 1-BENZYL-4-(5,6-DIMETHOXY-1-INDANON)-2-YL) METHYL PIPERIDINE HYDROCHLORIDE (DONEPEZIL HCl)**

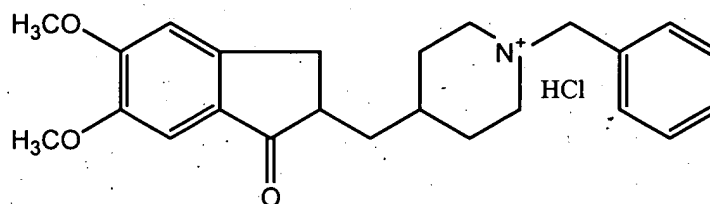
Cross-Reference to Related Applications

[0001] This application is continuation-in-part of U.S. Application Serial No. 10/365,717, filed February 12, 2003, which is entirely incorporated herein by reference.

Background of the Invention

Field of the Invention

[0002] This invention relates to a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride (Donepezil HCl) of the formula 1.



Formula 1

[0003] Compound of the formula 1 commonly known as Donepezil HCl is used for treatment of Central Nerve System (CNS) disorders.

Description of the Related Art

[0004] U.S. Patent No. 4895841 describes preparation of Donepezil HCl by reacting 5,6-dimethoxy-1-indanone with 1-benzyl-4-formylpiperidine in the presence of a strong base such as lithium diisopropyl amide followed by reduction with palladium carbon catalyst (Examples 3 and 4). Overall yield of Donepezil HCl is reported to be 50.8% (62% x 82%).

[0005] U.S. Patent No. 5,606,064 teaches the preparation of Donepezil HCl by the reaction of 5,6-dimethoxy-1-indanone with pyridin-4-aldehyde. The resulting 5,6-dimethoxy-2-(pyridin-4-yl)methyleneinda-1-one is reacted with benzyl bromide to afford 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-ylidene] methyl pyridinium bromide which on

reduction with platinum oxide catalyst afforded Donepezil HC1. (Examples 2, 4 and 6). Overall yield of Donepezil HC1 58.5% (87% x 83% x 81%).

[0006] PCT Publication No. WO 97/22584 reports preparation of Donepezil HC1 by reacting pyridine-4-aldehyde with malonic acid. The resulting 3-(pyridin-4-yl)-2-propionic acid was reduced with rhodium on carbon under hydrogen atmosphere to give 3-(piperidin-4-yl)-2-propionic acid which on reaction with methyl chlorocarbonate gave 3-[N-(methoxycarbonyl)piperidin-4-yl]propionic acid. On reacting 3-[N-(methoxycarbonyl)piperidin-4-yl] propionic acid with oxalyl chloride, methyl 4-(2-chlorocarbonyl)ethyl piperidin-1-carboxylate is obtained which on reaction with 1,2-dimethoxy benzene in the presence of aluminum chloride afforded 4-[3-(3,4-dimethoxyphenyl)-3-oxopropyl]piperidin-1-carboxylate. On reacting 4-[3-(3,4-dimethoxyphenyl)-3-oxopropyl] piperidin-1-carboxylate with tetramethyl diamino methane, 4-[2-(3,4-dimethoxy benzoyl) allyl] piperidin-1-carboxylate is obtained which on treatment with sulphuric acid gave methyl 4-(5,6-dimethoxy-1-indanon-2-yl methyl)piperidin-1-carboxylate. On decarboxylating 4-(5,6-dimethoxy-1-indanon-2-yl methyl) piperidin-1-carboxylate, 5,6-dimethoxy-2-(piperidin-4-yl methyl)-1-indanone is obtained which on treatment with benzyl bromide afforded Donepezil HC1 (Example 1 to 6). Overall yield of Donepezil HC1 19.3% (70% x 84% x 100% x 68% x 79% x 61%).

[0007] U.S. Patent No. 6,252,081 teaches the preparation of Donepezil HC1 by the reaction of 1-indanone derivative with carbonate ester. The resulting 2-alkoxycarbonyl-1-indanone derivative is halogenated with (4-pyridyl) methyl or a salt thereof and decarboxylated successively to give 2-(4-pyridyl)methyl-1-indanone derivative. On reacting the 2-(4-pyridyl) methyl-1-indanone derivative with benzyl bromide, their quaternary ammonium salts are formed, which on reduction with platinum oxide catalyst gives Donepezil HC1 (Examples 1 to 3). Overall yield of Donepezil HC1 82% (98% x 85% x 100% x 99%).

[0008] The prior art processes employs 1-benzyl-4-formyl piperidine as starting material whose synthesis is low yielding and involves use of lithium diisopropyl amide. The reaction of 1-benzyl-4-formyl piperidine with 5,6-dimethoxy-1-indanone also involves use of lithium diisopropyl amide and cryogenic temperatures which are expensive and are not

economically viable. Lithium diisopropyl amide is toxic and needs to be carefully handled. Many a time selective reduction of double bond to yield 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride is difficult to achieve. Besides, the selective reduction of double bond to give 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride is many a time coupled with formation of side products which are difficult to separate. Yield of the product is also affected due to the formation of the side products. Use of oxalyl chloride chemistry is difficult for scale up. Besides the oxalyl reaction also involves many protection deprotection chemistry and the overall yield is very low. Raw materials like methyl chlorocarbonate or tetramethyl diaminomethyl are expensive and difficult to source commercially. The prior art processes are also time consuming and difficult to carry out as they involve many steps.

#### Summary of the Invention

[0009] One embodiment is to provide a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride which eliminates formation of byproducts and gives high yield of the product and is efficient and economical.

[0010] Another embodiment is to provide a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride which employs less number of reaction steps and is less time consuming and easy and convenient to carry out.

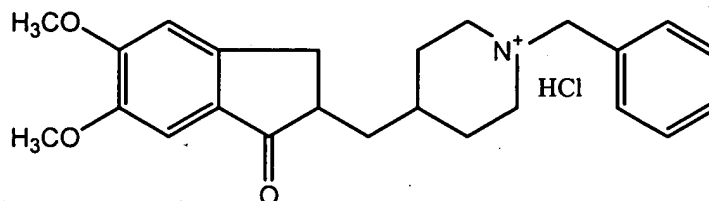
[0011] Another embodiment is to provide a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride which eliminates use of hazardous reagents and is safe to carryout.

[0012] Another embodiment is to provide a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride which employs cheaper and easily available raw materials.

[0013] Another embodiment is to provide a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride which is suitable for industrial scale up.

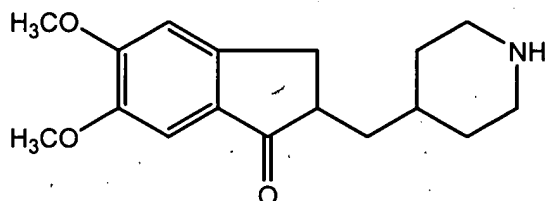
### Detailed Description of the Preferred Embodiment

[0014] According to an embodiment, there is provided a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methylpiperidine hydrochloride (Donepezil HCl) of the formula I



Formula I

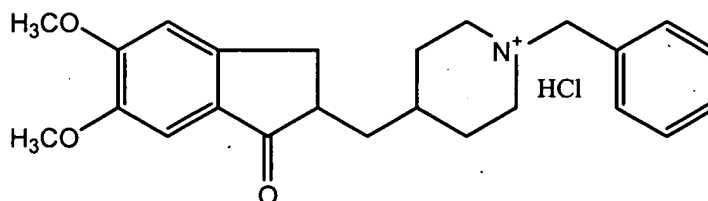
comprising hydrogenating 5,6-dimethoxy-2-(pyridin-4-yl) methylene inda-1-one with a noble metal oxide catalyst in an organic solvent at 20-50°C and 10-45 psi gauge pressure to form 4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine of the formula II



Formula II

which is alkylated with an alkylating agent in an organic solvent at 20-80°C.

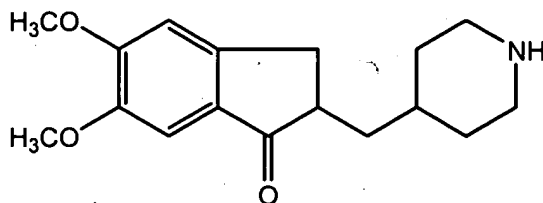
[0015] According to another embodiment, there is also provided a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methylpiperidine hydrochloride (Donepezil HCl) of the formula I



Formula I

comprising hydrogenating 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one with a noble metal catalyst or a non-oxide derivative of a noble metal catalyst in a solvent at 20-

100°C and 10-90 psi gauge pressure to form 4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine of the Formula II



Formula II

which is alkylated with an alkylating agent in an organic solvent at 20-80°C.

[0016] The organic solvent used in the hydrogenation of compound of the formula II with a noble metal oxide catalyst may be tetrahydrofuran, methanol or acetic acid or combination thereof preferably acetic acid:methanol mixture. Suitable solvents used in the hydrogenation of compound of the formula II with a noble metal catalyst or a non-oxide derivative of a noble metal catalyst may be C<sub>1</sub>-C<sub>4</sub> aliphatic alcohol, organic acid, dilute HCl, ethyl acetate, aliphatic ketone, or mixtures thereof. Preferably, the suitable solvent used with a noble metal catalyst or a non-oxide derivative of a noble metal catalyst is acetic acid.

[0017] The noble metal oxide catalyst used in hydrogenation may be platinum or palladium oxide, preferably platinum dioxide.

[0018] A noble metal catalyst used in hydrogenation may be palladium, rhodium, or ruthenium metal. A non-oxide derivative of a noble metal catalyst may also be used, such as a chloride or a sulphate of a noble metal selected from the group consisting of palladium, rhodium, and ruthenium.

[0019] The noble metal catalyst or non-oxide derivative of a noble metal catalyst can be supported on a carrier, such as carbon, calcium carbonate, barium sulphate, or alumina. A preferred carrier is carbon.

[0020] A preferred noble metal catalyst is palladium. A preferable condition for hydrogenation with a noble metal catalyst is 10% concentration of palladium on carbon.

[0021] Preferably hydrogenation using a noble metal oxide catalyst is carried out at 25-40°C and 25-40 psi gauge. Preferably hydrogenation using a noble metal catalyst or a non-oxide derivative of a noble metal catalyst is carried out at 70-80°C and 45-55 psi gauge.

Preferably hydrogenation using a noble metal catalyst or a non-oxide derivative of a noble metal catalyst is carried out at about 75°C and about 50 psi gauge.

[0022] The alkylating agent may be benzyl bromide or benzyl chloride, preferably benzyl bromide.

[0023] The organic solvent used in the alkylation reaction may be methylenedichloride, triethyl amine or mixtures thereof preferably methylene dichloride and triethyl amine mixture.

[0024] Preferably the alkylation is carried out at 20-80°C, more preferably at 30-40°C.

[0025] The process of preferred embodiments eliminates formation of byproducts and gives high yield of the product (about 92%). It employs cheaper and easily available raw materials and eliminates use of hazardous reagents. It is, therefore, efficient and economical and safe to carryout. It comprises only two steps and is, therefore, less time consuming and is easy and convenient to carryout. For the above reasons, it is also suitable for industrial scale up.

[0026] The following examples are illustrative of the invention but not limitative of the scope thereof.

### Example 1

#### 4-[5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine

[0027] 10 g (0.035 mole) 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one and 1 g Platinum dioxide were suspended in acetic acid-methanol mixture (200 ml: 200 ml) at room temperature and 30 psi gauge for six hours. Platinum dioxide was filtered off and the filtrate was concentrated. The residue was treated with 10% sodium hydrogen carbonate solution and the solution was extracted three times with methylene dichloride, dried and concentrated. Yield 10.1 g (99%). Corresponding HC1, mp 248 - 250°C, lit. mp 249-250°C, <sup>1</sup>H NMR (base, 200 MHz CDC1<sub>3</sub>) δ (ppm) 7.1 (s, 1H), 6.9 (s, 1H), 3.9 (s, 1H), 3.8 (s, 3H), 3.0-3.2 (m, 3H), 2.6-2.7 (m, 4H), 2.2 (bs, 1H, exchanges with D<sub>2</sub>O), 1.6-1.7 (m, 4H), 1.2-1.3 (m, 3H).

## Example 2

### 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride

[0028] 10g (0.0346 mol) of 4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine was dissolved in 100 ml methylene dichloride followed by 6.5 g benzyl bromide and 13 g triethyl amine. The reaction mixture was refluxed for four hours. The reaction mixture was filtered off and the filtrate was concentrated to yield 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine free base which was redissolved in 100 ml methanol followed by addition of 10 ml methanolic - HCl (10%). The reaction mixture was cooled to 10° and the resulting solid was filtered and washed with cooled methanol.

[0029] Yield 13.16g (92%). Mp 210-212°. <sup>1</sup>H NMR (200 MHz CDCl<sub>3</sub>) δ (ppm) 7.4 (m, 5H), 6.9 (s, 1H), 4.0 (s,3H), 3.9 (s,3H), 3.5 (s,2H), 3.2 (dd, 1H), 2.9 (d,2H), 2.7 (m, 2H), 2.0-1.4 (m,9H). Overall yield 95.5% (99% x 92%).

## Example 3

### 4-[(5,6-Dimethoxy-1-indanon)-2-yl] methyl piperidine

[0030] 10 g (0.035 mole) of 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one and 1 g palladium on carbon (10%) were suspended in acetic acid (300 ml) at 50 psi and 75°C for 4 hrs. Palladium was filtered off and the filtrate was concentrated. The residue was treated with 10% aqueous sodium hydrogen carbonate solution and the solution was extracted 3 times with dichloromethane (3x100ml), dried over sodium sulphate and concentrated to dryness. Yield of 4-[(5,6-Dimethoxy-1-indanon)-2-yl] methyl piperidine was 10.1 g (99%). Corresponding HCl of 4-[(5,6-Dimethoxy-1-indanon)-2-yl] methyl piperidine had mp 248-250°C, lit. mp 249-250°C (synthesis adopting different route of USP-4,895,841).

[0031] <sup>1</sup>H NMR (base, 200 MHz CDCl<sub>3</sub>) δ (ppm) 7.1(s,1H), 6.9 (s,1H), 3.9 (s,3H), 3.8 (s,3H), 3.0-3.2 (m,3H), 2.6-2.7 (m,4H), 2.2 (bs,1H, exchanges with D<sub>2</sub>O), 1.6-1.7 (m,4H), 1.2-1.3 (m,3H).